

STATE-OF-THE-ART PAPER

Current Concepts of Integrated Coronary Physiology in the Catheterization Laboratory

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Over the last 15 years, the use of invasive coronary physiology in the catheterization laboratory has demonstrated favorable outcomes for decision making in patients with intermediate single-vessel stenoses, complex bifurcation and ostial branch stenoses, multivessel coronary artery disease, and left main stenoses. A recent large multicenter study (FAME [FFR versus Angiography for Multivessel Evaluation]) found that a physiologically-guided approach was superior to the standard angiographically-guided approach for percutaneous revascularization in patients with multivessel coronary artery disease. This review addresses selected pertinent concepts and studies supporting the integration of coronary physiology in the catheterization laboratory for optimal patient outcomes. (J Am Coll Cardiol 2010;55:173-85)

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Patients with coronary artery disease (CAD) and myocardial ischemia refractory to medical therapy frequently undergo revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). When gauging whether ischemia is responsible for symptoms, clinicians routinely integrate coronary physiology into the treatment plan, employing any of a number of stress challenges to coronary blood flow through exercise or pharmacologic stimulation, and observe the associated electrical, perfusion, or functional myocardial responses. In the last decade, invasive cardiologists have used sensor-tipped angioplasty guidewires in the catheterization laboratory (cath lab) to measure coronary blood flow and pressure across stenotic artery segments to determine the ischemic potential of a specific stenosis.

Integrating invasive coronary physiology with angiography has become routine in many but not all cath labs. Indeed, in the last 15 years, invasive coronary physiologic studies have demonstrated favorable outcomes for decision making in patients with intermediate single-vessel stenoses (1-3), bifurcation and ostial branch stenoses (4,5), multivessel CAD, and left main stenoses (6-11). The following discussion will review selected pertinent concepts and studies, with focus on pressure measurements, supporting the integration of coronary physiology in the cath lab for optimal patient outcomes.

Rationale for Coronary Physiology in the Cath Lab

The rationale for physiologic lesion assessment is based on 2 simple facts: 1) the decision to revascularize relies primarily on the hemodynamic significance of a lesion; and 2) coronary angiography frequently fails to identify the accurate hemodynamic significance of coronary stenoses, particularly those between 30% and 80% diameter stenosis (12,13). This failing has been documented repeatedly by the necessity for stress testing to clarify the functional (i.e., ischemic) response to narrowings seen on coronary angiography. Despite sophisticated imaging employing densitometry, rotational angiography, and 3-dimensional reconstruction, the anatomic complexity of an atherosclerotic lumen does not reliably reflect the physiologic impact on the circulation (Fig. 1). Coronary angiography produces 2-dimensional silhouette images of the 3-dimensional vascular lumen. Because angiographic stenosis severity is reported as a ratio of the stenosis' minimal lumen diameter to the adjacent "normal" reference segment, accuracy is limited by the inability to identify both "diseased" and "normal" vessel segments, particularly in the setting of diffuse CAD. In addition, unlike intravascular ultrasound and computerized tomographic angiography, angiography does not provide vascular wall detail sufficient to characterize plaque size, length, and eccentricity. The eccentric lumen produces conflicting degrees of angiographic narrowing from different viewing angulations and introduces uncertainty related to lumen size and its relationship to coronary blood flow (14). Moreover, a long, moderate narrowing can be as or more hemodynamically significant than a short, focal severe narrowing (Fig. 2). Additional artifacts including contrast streaming, branch overlap, vessel foreshortening, calcifications, and ostial origins further contribute to the uncertainty of the angiographic interpretation.

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Abbreviations and Acronyms

ACS	= acute coronary syndrome
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
Cath lab	= catheterization laboratory
CFR	= coronary flow reserve
FFR	= fractional flow reserve
MACE	= major adverse cardiac events
MI	= myocardial infarction
Pa	= aortic pressure
PCI	= percutaneous coronary intervention
Pd	= mean pressure distal to a stenosis
QCA	= quantitative coronary angiography
SPECT	= single-photon emission computed tomography
TIMI	= Thrombolysis In Myocardial Infarction

Despite numerous attempts to evaluate complex anatomy, the angiographer is still confronted with a visual dilemma in which no single view, or even multiple views, provides an answer. In this setting, coronary physiologic data either by noninvasive stress or invasive physiologic testing is required to confirm ischemia. If the noninvasive approach is taken after angiography, a positive test will require repeat catheterization for PCI, an inefficient approach for both patients and the health care system. In contrast, invasive physiologic testing at the time of angiography can direct appropriate revascularization in a single setting, facilitating optimal patient care.

Fractional Flow Reserve (FFR) Theory and Measurement

FFR is defined as the ratio of (i.e., percent of normal) flow in the stenotic artery to the flow in the same artery in the theoretic ab-

sence of the stenosis (2). Because flow is proportional to pressure, if resistance is minimal and constant (Ohm's Law), pressure can be used as a surrogate of flow during maximal hyperemia, which minimizes resistance. Pressure in a normal coronary artery is equal to aortic pressure (Pa). Thus, FFR is simply calculated as the ratio of mean pressure distal (Pd) to a stenosis to Pa during maximal hyperemia (Fig. 3). In contrast to coronary flow reserve (CFR) (the ratio of hyperemic to basal blood flow), FFR has a clear normal value of 1. This is because normal epicardial resistance is trivial, and Pa is transmitted completely to the distal artery, making both the numerator and denominator the same value. An FFR of 0.75 means that the stenotic vessel only provides 75% of the normal expected flow in the theoretical absence of the stenosis. In addition, FFR is a specific index for the epicardial stenosis. Its derivation attempts to exclude the confounding influence of the microcirculation, changes in hemodynamics, or contractility (15). Unlike CFR, FFR is minimally influenced by conditions known to alter baseline or maximal hyperemic myocardial blood flow.

The methods of translesional pressure measurement have been previously reviewed in detail (16–18). In brief, following diagnostic angiography in the cath lab and using a technique identical to that of routine angioplasty, a 0.014-inch pressure sensor angioplasty guidewire is inserted through a guiding catheter and into the target artery. Before crossing the stenosis, the sensor wire's

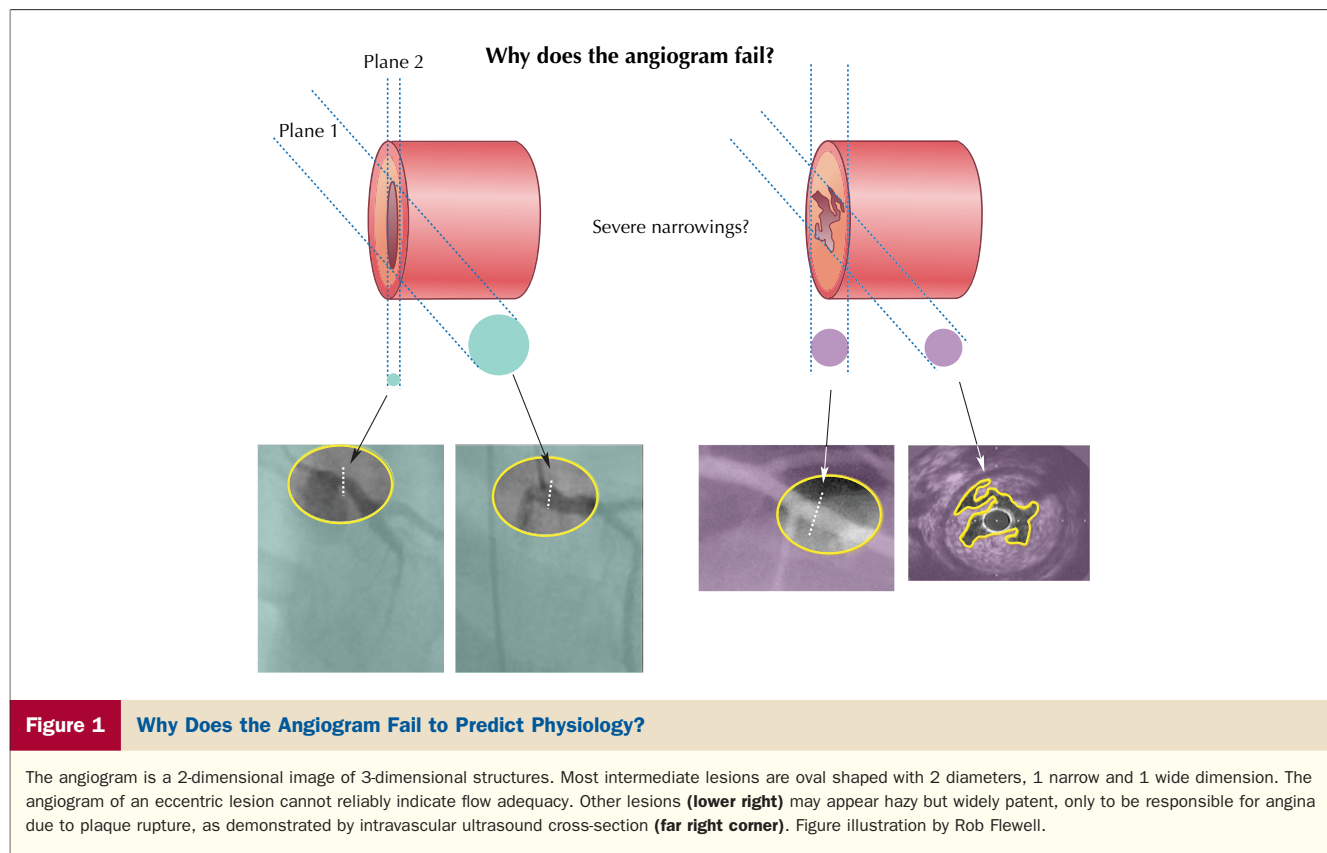
pressure signal is first matched to the aortic (guide catheter) pressure. The pressure wire is then advanced across the lesion. Coronary hyperemia is then induced, usually with intravenous or intracoronary adenosine (19), though papaverine, adenosine triphosphate, or selective adenosine 2A agonists can also be used (20). The Pd and Pa are continuously recorded. FFR is then calculated as Pd/Pa at maximal hyperemia, the nadir of Pd. An example of FFR is shown in Figure 4.

To assess serial lesions or diffuse CAD, the pressure wire can be pulled back steadily from the distal to proximal vessel segments during continuous hyperemia induced by intravenous adenosine, papaverine, or adenosine 2A agonists. The pressure pullback curve can demonstrate either an abrupt change in distal pressure across a focal narrowing or the gradual pressure recovery of diffuse disease without focal obstructions. Tandem lesions in a vessel can also be assessed by the pullback recording, treating the most severe gradient-inducing lesion first and then reassessing the remaining lesion. In the case of post-stent assessment, intravascular ultrasound is recommended for stent apposition because FFR can be normalized with unappreciated suboptimal stent deployment.

FFR has prognostic value for late events after bare-metal stenting (21). Furthermore, FFR measurement of lesions in the cath lab can complement the anticipated stent diameter in choosing which lesions may be optimally treated with bare-metal stenting with favorable outcomes (22).

Validation and Threshold of Ischemia

FFR values <0.75 are associated with ischemic stress testing in numerous comparative studies with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%). FFR values >0.80 are associated with negative ischemic results with a predictive accuracy of 95%. Reports from single stress testing comparisons and variations in testing and patients have produced a small zone of FFR uncertainty (0.75 to 0.80), the use of which requires clinical judgment. A meta-analysis of 31 studies (23) comparing the results of FFR to quantitative coronary angiography (QCA) and/or noninvasive imaging of the same lesions reported (18 studies, 1,522 lesions) found that QCA had a random effects sensitivity of 78% and specificity of 51% against FFR (<0.75 cutoff). Compared with noninvasive imaging (21 studies, 1,249 lesions), receiver-operating characteristic estimates were similar for comparisons of FFR with perfusion scintigraphy (976 lesions, sensitivity 75%, specificity 77%) and dobutamine stress echocardiography (273 lesions, sensitivity 82%, specificity 74%). Given the variances of sensitivity, specificity, positive and negative predictive accuracy among patients, and types of stress testing, it is not surprising that, unlike the initial validation study (1) comparing FFR with 3 different stress tests in the same patient before and after PCI, this meta-analysis showed only modest concordance of FFR with noninvasive imaging tests. Furthermore, because perfusion scintigraphy



compares relative and not absolute myocardial flow in different coronary beds, scintigraphy, although considered the clinical gold standard of ischemia, has limitations in identifying the hemodynamic significance of individual lesions in patients with multivessel CAD (24,25). Similarly, on stress echocardiography, severe ischemia in one region may mask the consequences of a less severe albeit hemodynamically significant lesion in another region. In contrast to noninvasive tests, FFR is a vessel-specific index of ischemia. Table 1 is a summary of important validation studies of FFR (26–36).

Although no longer used for stenosis assessment, a Doppler-tipped sensor guidewire can measure CFR. An abnormal CFR (<2.0) corresponded to reversible myocardial perfusion imaging defects with high sensitivity (86% to 92%), specificity (89% to 100%), predictive accuracy (89% to 96%), and positive and negative predictive values (84% to 100% and 77% to 95%, respectively) (37). The uncertainty of the microcirculatory contribution to an abnormal CFR makes CFR alone less useful for epicardial lesion assessment (37). Combined pressure and flow data have produced a novel set of invasive physiologic tools for epicardial lesion assessment such as hyperemic stenosis resistance and for microvascular assessment such as index of microcirculatory resistance (IMR) (38) and hyperemic myocardial resistance. Defined as the hyperemic change in pressure across a stenosis divided by the hyperemic distal velocity, hyperemic stenosis resistance may have better predictive value than FFR for detecting noninvasive ischemia (34,39). A sum-

mary of coronary physiologic measurements and derivations is provided in Table 2. The American College of Cardiology and the American Heart Association have produced a consensus statement and guidelines for the physiologic assessment of CAD in the cardiac cath lab (37).

Outcome of Using FFR for Intermediate Lesions

A number of registries have reported low adverse cardiac event rates at 1 to 2 years after deferral (better stated as nonperformance) of PCI in patients with moderate stenoses and non-ischemic FFR. The DEFER (FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses) study randomized 325 patients scheduled for PCI into 3 groups and reported the 5-year outcomes (40). If FFR was ≥ 0.75 , patients were randomly assigned to the deferral group ($n = 91$, medical therapy for CAD) or the PCI performance group ($n = 90$, PCI with stents). If FFR was <0.75 , PCI was performed as planned, and patients were entered into the reference group ($n = 144$). Complete follow-up was obtained in 98% of patients. Overall, the event-free survival was not different between the deferred and performed groups (80% and 73%, respectively, $p = 0.52$), and both were significantly better than in the reference group (63%, $p = 0.03$). The composite rate of cardiac death and acute myocardial infarction in the deferred, performed, and reference groups was 3.3%, 7.9%, and 15.7%, respectively ($p = 0.21$ for deferred vs. performed and $p = 0.003$ for reference vs. both of the deferred and performed

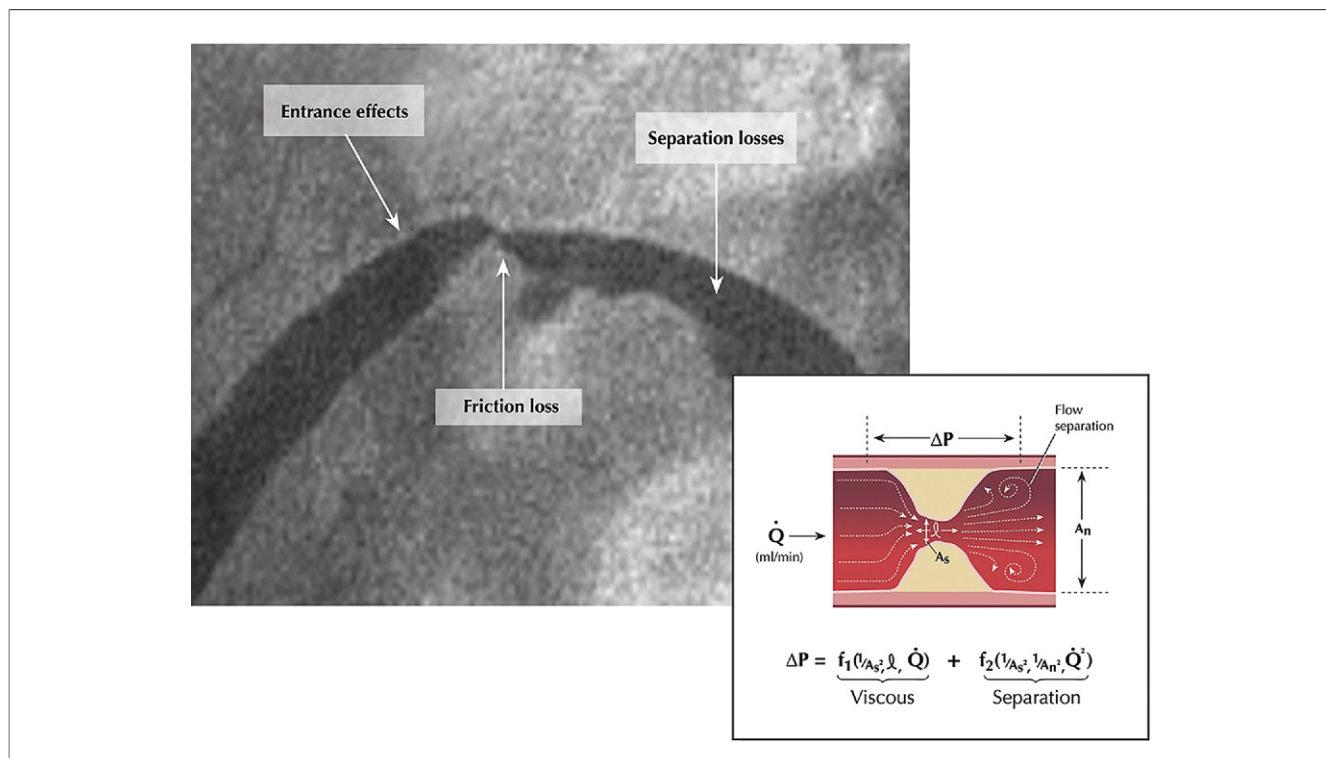


Figure 2 Factors Producing Resistance to Coronary Blood Flow

The angiographic 2-dimensional images cannot account for the multiple factors that produce resistance to coronary blood flow and loss of pressure across a stenosis. The eccentric and irregular stenosis (**upper panel**) shows **arrows** designating entrance effects, friction, and zones of turbulence accounting for separation energy loss. The calculation of pressure loss (ΔP) across a stenosis (**lower right panel**) incorporates length (l), areas stenosis (A_s), reference area (A_n), flow (Q), and coefficients of viscous friction and laminar separation (f_1 and f_2) as contributors to resistance and hence pressure loss. Figure illustration by Rob Flewell.

groups) (Fig. 5). The percentage of patients free from chest pain on follow-up was not different between the deferred and performed groups. The 5-year risk of cardiac death or myo-

cardial infarction (MI) in patients with normal FFR is <1% per year and is not decreased by stenting. Treating patients guided by FFR is associated with a low event rate, comparable to event rates in patients with normal noninvasive testing (Table 3) (41–50).

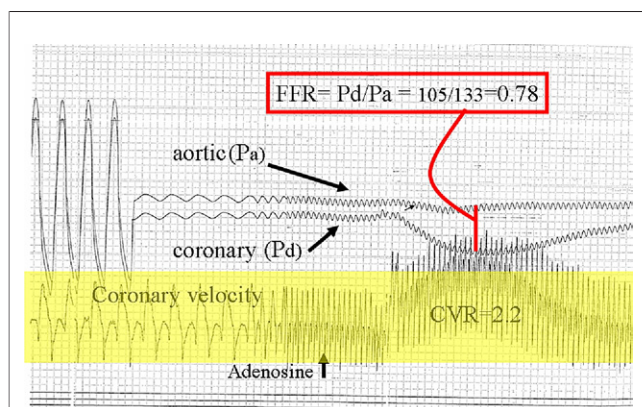


Figure 3 Pressure Signals Used to Calculate FFR

Phasic and mean pressure signals used to measure fractional flow reserve (FFR), calculated as the ratio of distal coronary pressure (P_d) to aortic pressure (P_a) at maximal hyperemia, which is equal to 0.78 in this example. For reference to coronary flow, a velocity signal is shaded and shown at the bottom to identify the time of maximal hyperemia. The velocity signal is only available in combined sensor wire studies. Courtesy of Dr. Bernard DeBruyne. CVR = coronary vasodilatory reserve.

Multivessel CAD

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (51) reminded us that PCI offers no benefit over medical therapy with respect to death or MI reduction in low- to intermediate-risk patients with multivessel CAD. However, PCI reduced major adverse events in the subset of the COURAGE population that had significant ischemia (52). In concert with the COURAGE study, it must be recognized that not all multivessel angiographic CAD is physiologically equivalent CAD. Using FFR to assess all 3 vessels, Sant’Anna et al. (53) have shown that the incidence of “significant” 3-vessel angiographic CAD drops from 27% to 9%, 2-vessel drops from 43% to 17%, and single-vessel disease increases from 30% to 60%, simplifying decision making in this difficult patient group.

Early nonrandomized studies demonstrated the benefit of FFR guidance in patients with multivessel CAD. Berger

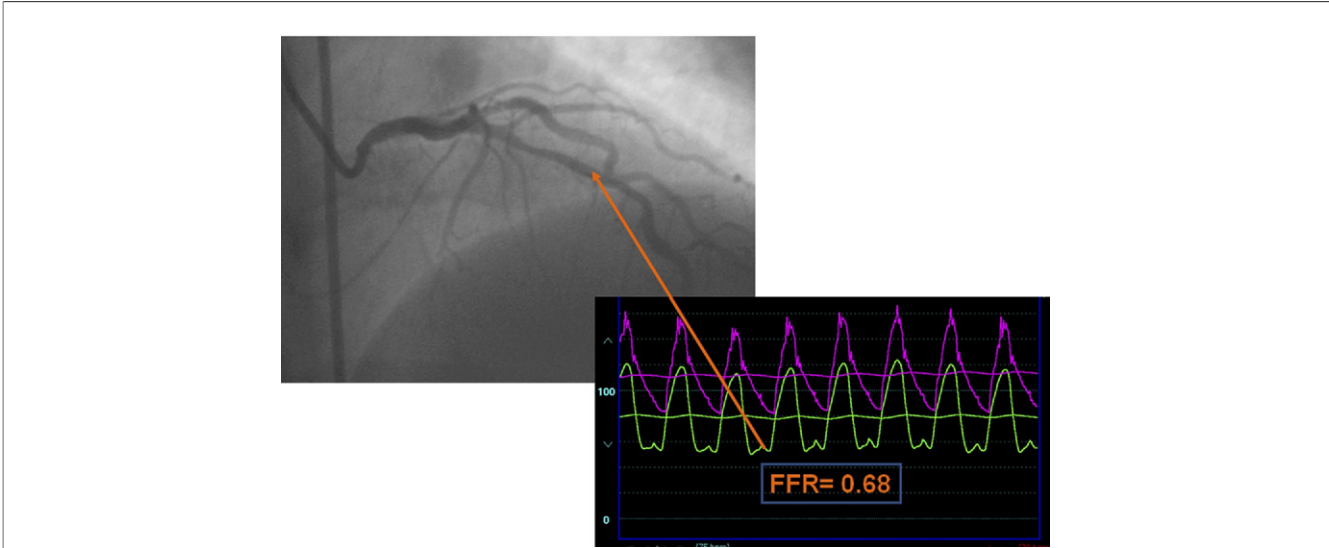


Figure 4 Cine Angiographic Frame of Intermediate Left Anterior Descending Coronary Artery Stenosis

Pressure wire transducer located at **arrow**. Lower panel shows phasic and mean aortic and distal coronary pressure with significant pressure loss during hyperemia. Fractional flow reserve (FFR) is $75/110 = 0.68$.

et al. (54) showed a reduction in major adverse cardiac events in 102 patients with multivessel CAD with planned PCI of at least 2 vessels. In 113 coronary arteries with baseline FFR of 0.57 ± 0.13 , PCI was performed, and in 127 coronary arteries with an FFR >0.75 (FFR 0.86 ± 0.06), PCI was not performed. Overall major adverse cardiac events (MACE) occurred in 9% of patients after 12 months and 13% after 36 months. In the nontreated vessels, 8 (6.3%) MACE were reported, whereas 14 (12.3%) MACE were related to 1 of the initially PCI-treated coronary arteries. Similarly, in another nonrandomized,

single-center trial, FFR-guided PCI (FFR-PCI) was compared with angiographic-guided PCI (Angio-PCI) in 137 patients with multivessel CAD (55). PCI was performed for all stenoses with an FFR <0.75 . Compared with the FFR-PCI group, there were more vessels per patient treated in the Angio-PCI group (2.27 ± 0.50 vs. 1.12 ± 0.30 vessels) at a higher cost ($\$3,167 \pm \$1,194$ vs. $\$2,572 \pm \934 , respectively; $p < 0.001$). The 30-month Kaplan-Meier event-free survival was significantly higher in the FFR-PCI group than in the Angio-PCI group (89% vs. 59%; $p < 0.01$).

Table 1 Physiologic Measurements and Noninvasive Stress Test Results

Index	Author (Ref. #)	n	Ischemic Test	BCV	Accuracy
FFR					
	Pijls et al. (2)	60	X-ECG	0.74	97
	DeBruyne et al. (26)	60	X-ECG/SPECT	0.72	85
	Pijls et al. (1)	45	X-ECG/SPECT/pacing/DSE	0.75	93
	Bartunek et al. (27)	37	DSE	0.68	90
	Abe et al. (28)	46	SPECT	0.75	91
	Chamuleau et al. (29)*	127	SPECT	0.74	77
	Caymaz et al. (30)	40	SPECT	0.76	95
	Jimenez-Navarro et al. (31)	21	DSE	0.75	90
	Usui et al. (32)	167	SPECT	0.75	79
	Yanagisawa et al. (33)	167	SPECT	0.75	76
	Meuwissen et al. (34)	151	SPECT	0.74	85
	DeBruyne et al. (35)	57	MIBI-SPECT post-MI	0.78	85
	Samady et al. (36)	48	MIBI-SPECT post-MI	0.78	85
H-SRv					
	Meuwissen et al. (34)	151	SPECT	0.80	87

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BCV = best cut-off value (defined as the value with the highest sum of sensitivity and specificity); DSE = dobutamine stress echocardiography; MI = myocardial infarction; SPECT = single-photon emission computed tomography; X-ECG = exercise electrocardiogram.

Table 2 Integrated Coronary Physiologic Measurements in the Catheterization Laboratory

FFR

Derivation: $FFR = Q_{sten}/Q_{normal}$ at maximal hyperemia. Q = flow, sten = stenotic artery, normal = theoretic same artery without stenosis

$$Q_{sten} = P_{aorta}/Resistance_{sten}$$

$$Q_{normal} = P_{aorta}/Resistance_{sten}, \text{ then } Q_{sten}/Q_{normal} = P_{sten}/P_{aorta}$$

$$\text{Hence } FFR = P_{distal \text{ to stenosis}}/P_{aorta}$$

(complete derivation includes venous pressure Pv as $FFR = P_{distal \text{ to stenosis}} - Pv / P_{aorta} - Pv$, see Pijls et al. [2])

Features: nonischemic threshold range > (0.75–0.80); normal value of 1.0 for every artery and every patient; epicardial lesion specific; linear relation with relative maximum blood flow; independent of hemodynamic alterations; value that accounts for total myocardial blood flow, including collaterals; highly reproducible; high spatial resolution (pressure pullback recording)

CFVR

Derivation: $CFVR = Q_{hyperemia}/Q_{base}$. Q = velocity if cross-sectional area unchanged during hyperemia

Features: Nonischemic threshold range of CFR >2.0; coronary flow reserve in nonobstructed vessels assesses microvascular integrity; useful for studies of coronary endothelial function; accurate estimation of volumetric flow when vessel cross-sectional area available

Combined pressure and flow velocity measurements: for example, HSR

$$\text{Derivation: } HSR = P_{aorta} - P_{distal \text{ to stenosis}}/hyperemic \text{ Q}$$

Features: Separate assessment of stenosis and microvascular resistances; allows construction of pressure flow curves (assessment of compliant lesions, hemodynamic gain after PCI)

For Stenosis Resistance Index: Nonischemic threshold values <0.8 mm Hg/cm/s; normal value of 0; lesion specific; highly reproducible; high sensitivity; useful in cases of discordance between CFR and FFR

CFR = coronary flow reserve; CFVR = coronary flow velocity reserve; FFR = fractional flow reserve; HSR = hyperemic stenosis resistance; PCI = percutaneous coronary intervention.

These studies (54,55) led to the larger prospective randomized, multicenter FAME (FFR versus Angiography for Multivessel Evaluation) trial (11). Tonino et al. (11) for the FAME study investigators addressed the hypothesis that a physiologically-guided PCI approach (FFR-PCI) was superior to conventional Angio-PCI in patients with multivessel CAD. Twenty centers in Europe and the U.S. randomly assigned 1,005 patients with multivessel CAD undergoing PCI with drug-eluting stents to 1 of the 2 strategies. Operators selected all indicated lesions in advance of randomization for stenting by visual angiographic appearance (>50% diameter stenosis). For the FFR-PCI group, all lesions had FFR measurements and were only stented if the FFR was <0.80. The primary end points of death, MI, and repeat revascularization (CABG or

PCI) were obtained at 1 year. Of the 1,005 patients, 496 were assigned to the Angio-PCI group, and 509 were assigned to the FFR-PCI group. Clinical characteristics and angiographic findings were similar in both groups. The Syntax (Synergy between PCI with Taxus and Cardiac Surgery) scores for gauging risk in multivessel disease involvement were identical at 14.5, indicating low-intermediate risk patients.

Despite identifying in advance 3 angiographically indicated lesions per patient for stenting, compared with the Angio-PCI group, the FFR-PCI group used fewer stents per patient (1.9 ± 1.3 vs. 2.7 ± 1.2 , $p < 0.001$), less contrast (272 ml vs. 302 ml, $p < 0.001$), had lower procedure cost (\$5,332 vs. \$6,007, $p < 0.001$), and shorter hospital stay (3.4 days vs. 3.7 days, $p = 0.05$). More

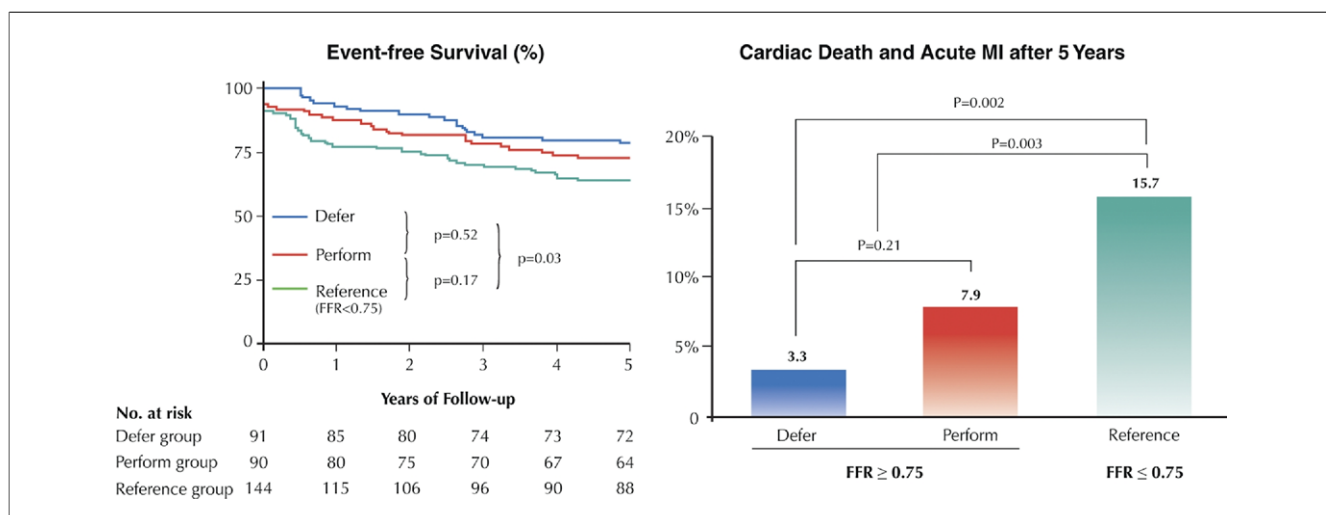


Figure 5 Data From the DEFER Study: 5-Year Follow-Up Study

(Left) Event-free survival curves for the Defer, Perform, and Reference groups. (Right) Incidence of cardiac death/myocardial infarction (MI) for the 3 groups. Reprinted, with permission, from Pijls et al. (40).

Table 3 Outcomes After FFR-Based Deferral of Coronary Intervention in Intermediate Coronary Lesions

Index	Author (Ref. #)	n	Defer Value	MACE (%)	Follow-Up (Months)
FFR					
	Bech et al. (41)	100	0.75	8	18
	Hernandez Garcia et al. (42)	43	0.75	12	11
	Bech et al. (43)	60	0.75	12	24
	Bech et al. (6)*	24	0.75	21	29
	Rieber et al. (44)	47	0.75	13	12
	Chamuleau et al. (45)	92	0.75	9	12
	Rieber et al. (46)	24	0.75	8	12
	Leesar et al. (47)†	34	0.75	9	12
	Pijls et al. (40)	325	0.75	3	60
CFR					
	Kern et al. (48)	88	2.0	7	9
	Ferrari et al. (49)	22	2.0	9	15
	Chamuleau et al. (50)‡	143	2.0	6	12

Modified with permission from Kern MJ. Coronary physiology revisited: practical insights from the cardiac catheterization laboratory. *Circulation* 2000;101:1344–51. *Left main stenosis. †>unstable angina pectoris. ‡Multivessel disease.

MACE = major adverse cardiac events (principally rates of percutaneous coronary intervention; no significant rates of death/myocardial infarction); other abbreviations as in Table 2.

importantly, at 1-year follow-up, the FFR-PCI group had fewer MACE (13.2% vs. 18.4%, $p = 0.02$), fewer combined death or MI (7.3% vs. 11%, $p = 0.04$), and a lower total number of MACE (76 vs. 113, $p = 0.02$) compared with the Angio-PCI group (Fig. 6).

FAME used an FFR ischemic cutoff value of 0.80. It is possible that some lesions with FFR between 0.75 and 0.79 that had PCI could have been treated medically, but the outcomes still remained positive for the FFR-PCI strategy. The precise mechanisms of reduced end points in the FFR-guided arm of FAME are not known, but are likely associated with fewer implanted stents having fewer procedure-related early (e.g., side branch occlusion, additional troponin release) and late stent complications (e.g., subacute thrombosis, restenosis). This study is a substantial clinical validation of the preceding FFR outcome studies in single and multivessel disease patients from single centers and has important implications for managing CAD patients integrating physiology for the best long-term results. Figure 7 shows an example of a patient with multivessel disease treated on the basis of an FFR-guided PCI strategy.

Left Main Stenosis

Correct clinical assessment of left main stem CAD lesions is of pivotal importance. On the basis of angiographic information alone, this evaluation often cannot be done reliably. Limited data suggest that FFR supports decision making in equivocal left main disease. In a prospective single-center follow-up study, Bech et al. (6) studied 51 patients with intermediate or ambiguous left main CAD. If FFR was <0.75 , surgical revascularization (CABG) was recommended; if FFR was >0.80 , medical treatment for the left main with PCI elsewhere as indicated was performed. If FFR was in the “gray zone” (≥ 0.75 and ≤ 0.80), treatment was dependent on additional

individual criteria. Of 51 patients, CABG was performed in 27 patients (53%). The remaining 24 patients (47%) were treated nonsurgically. Estimated survival after 4 years of follow-up was 81% among CABG patients and 100% among patients in the nonsurgical group. Event-free survival was 66% in the CABG group and 69% in the nonsurgical group. In the largest cohort to date, Curtis et al. (56) studied 142 consecutive patients with intermediate left main coronary artery stenosis ($42 \pm 13\%$ diameter). Those patients with FFR >0.80 ($n = 82$) were treated medically; those patients with FFR <0.75 ($n = 60$) underwent CABG. MACE at 14 months’ follow-up was 13% and 7%, respectively ($p = 0.27$). Cardiac death or MI was also similar (6% and 7%, $p = 0.70$). FFR appears helpful in identifying patients with intermediate left main disease suitable for surgical revascularization or continued medical therapy, with excellent survival and low event rates (57). Figure 8 shows an example of a patient with moderate left main disease evaluated physiologically.

FFR and Ostial Branch Assessment

Ostial narrowings, especially in side branches within stents (called “jailed” branches), are particularly difficult to assess by angiography because of the overlap orientation relative to the parent branch, stent struts across the branch, and image foreshortening. Koo et al. (58) compared FFR with QCA in 97 “jailed” side branch lesions (vessel size >2.0 mm, percent stenosis $>50\%$ by visual estimation) after stent implantation. No lesion with $<75\%$ stenosis had FFR <0.75 . Among 73 lesions with $\geq 75\%$ stenosis, only 20 lesions (27%) were functionally significant. Koo et al. (58) also reported the 9-month outcome of FFR-guided side branch PCI strategy for bifurcation lesions. Of the 91 patients, side branch intervention was performed in 26 of 28 patients with FFR <0.75 . In this subgroup, FFR increased to >0.75

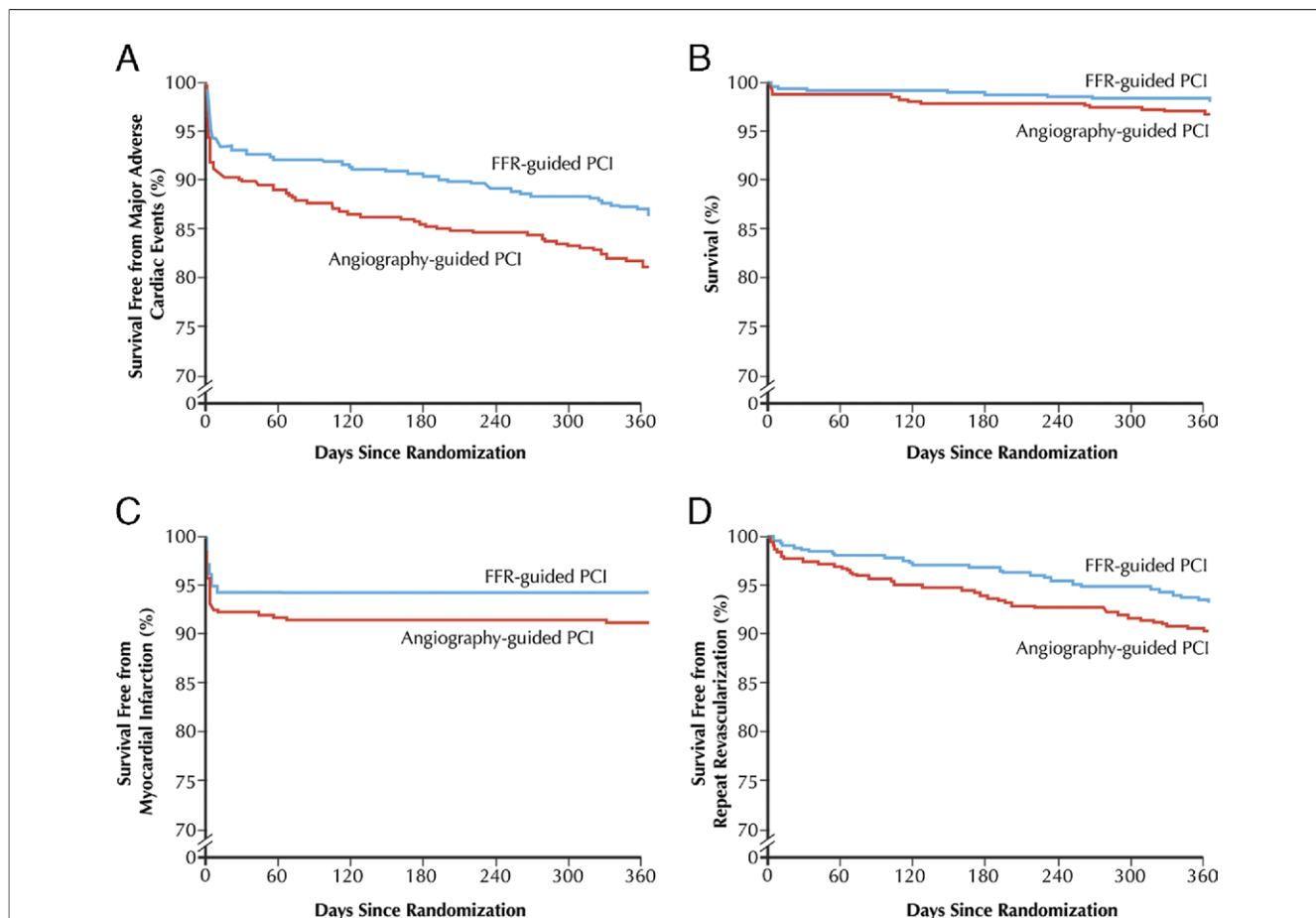


Figure 6 Data From the FAME Study: Kaplan-Meier Survival Curves for 1-Year Follow-Up of the FAME Patients

(A) Event-free survival for major adverse cardiac events was significant at 1 year. No differences in event-free survival for death (B), myocardial infarction (C), or coronary artery bypass grafting/percutaneous coronary intervention (PCI) (D). Reprinted, with permission, from Tonino et al. (11).

despite residual stenosis of $69 \pm 10\%$. At 9 months, functional restenosis was 8% (5 of 65), with no difference in events compared with 110 side branches treated by angiography alone (4.6% vs. 3.7%, $p = 0.7$) (Fig. 9). Measurement of FFR for ostial and side branch assessment identifies a minority of lesions that are functionally significant (4,5,58).

FFR and CABG Conduit Patency

Although most surgical recommendations for patients with multivessel disease are to bypass all lesions with $>50\%$ diameter narrowing, the patency rate of saphenous vein grafts on vessels with hemodynamically nonsignificant lesions has been questioned. Botman et al. (59) found that there was a 20% to 25% incidence of graft closure in 450 CABGs when placed on nonhemodynamically significantly stenosed arteries (preoperative FFR >0.80) at 1 year of follow-up (Fig. 10). Although the precise mechanisms of graft closure remain under study, it is postulated that coronary blood flow favors the lower resistance path through the native (relatively) nonobstructed arteries rather than vein grafts, with slower or com-

petitive graft flow promoting premature graft closure (60). In patients requiring CABG for multivessel revascularization, angiographic lesions of uncertain significance would benefit from FFR, providing prognostic information regarding potential of future bypass graft patency. FFR has serious implications for best long-term CABG outcomes.

FFR and Acute Coronary Syndrome (ACS)

The pathophysiology of the infarct-related artery and bed after MI is complex. Because of the dynamic nature of patients with ACS, particularly MI, the predictive ability of FFR has some theoretic limitations. In ACS, the microvascular bed in the infarct zone may not have uniform, constant, or minimal resistance. The stenosis may also evolve as thrombus and vasoconstriction abate. FFR measurements are not meaningful when angiographic reperfusion (i.e., Thrombolysis In Myocardial Infarction [TIMI] flow grade 3) has not been achieved in the artery. FFR has limited use in the infarct-related artery in the acute setting. However, FFR has value in lesion assessment in the

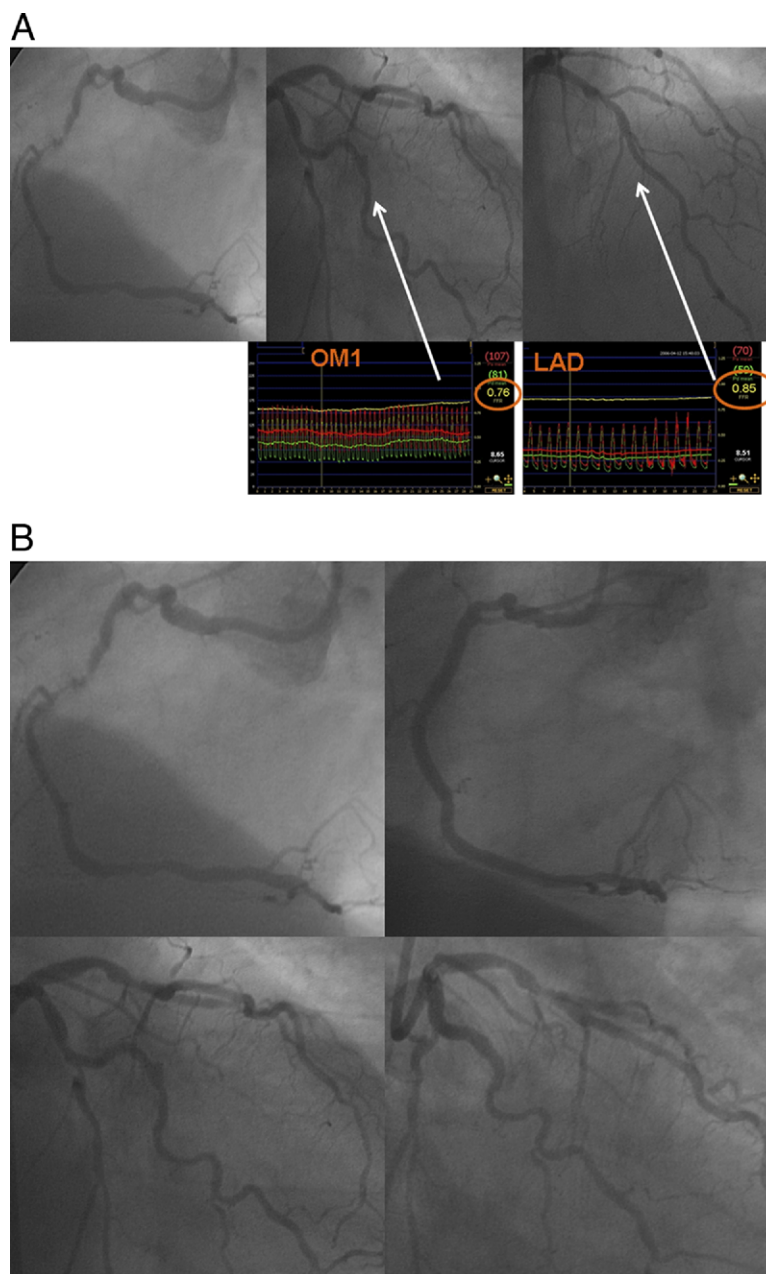


Figure 7 FFR in Multivessel PCI Decision Making

(A) Cine angiograms and FFR in a patient undergoing multivessel assessment. **(Left)** Right coronary artery with diffuse severe disease. **(Middle)** First obtuse marginal (OM1) shows FFR = 0.76. **(Right)** Left anterior descending artery (LAD) FFR = 0.85. Intervention on right coronary artery, OM, was performed. **(B)** Angiographic results of PCI guided by FFR. Abbreviations as in Figure 1.

recovery phase of MI and in the assessment of lesions in the remote noninfarct-related vessels.

To address the utility of measurements days after MI, DeBruyne et al. (35) compared single-photon emission computed tomography (SPECT) myocardial perfusion imaging and FFR obtained before and after PCI in 57 MI patients >6 days (mean 20 days) before evaluation. Patients with positive SPECT before PCI had a significantly lower

FFR than patients with negative SPECT (0.52 ± 0.18 vs. 0.67 ± 0.16 ; $p = 0.0079$), but a significantly higher left ventricular ejection fraction ($63 \pm 10\%$ vs. $52 \pm 10\%$; $p = 0.0009$) despite a similar percent diameter stenosis ($67 \pm 13\%$ vs. $68 \pm 16\%$; $p = \text{NS}$). The sensitivity and specificity of FFR of <0.75 to detect a defect on SPECT were 82% and 87%, respectively. When only truly positive and negative SPECT imaging was considered, the corresponding

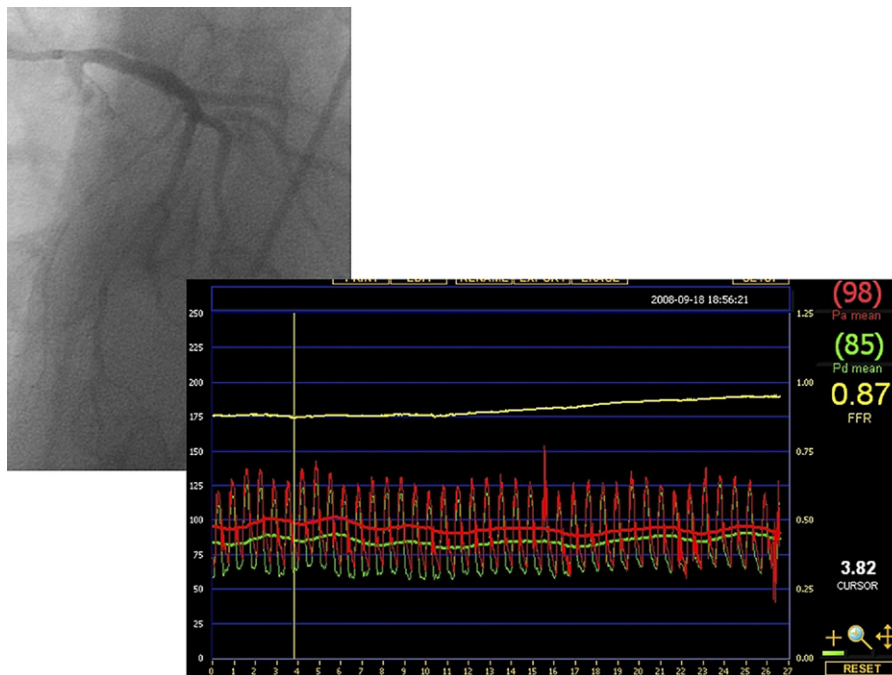


Figure 8 Cine Frame of Intermediate Left Main Narrowing

Fractional flow reserve (FFR) was 0.87. Medical therapy was recommended. Pa = aortic pressure; Pd = mean pressure distal to a stenosis.

values were 87% and 100% ($p < 0.001$). The best FFR cutoff for determining peri-infarct ischemia was 0.78. Of note, a significant inverse correlation was found between left ventricular ejection fraction and FFR ($r = 0.29$, $p = 0.049$), suggesting a relationship between FFR and the mass of viable myocardium. For patients who are >6 days after an infarction, FFR accurately reflects the hemodynamic sever-

ity of a lesion and its impact on myocardial perfusion despite the damaged microvasculature in the infarct bed.

In a similar study and relevant to clinical practice in the U.S., where AMI patients often present early for angiographic evaluation day 1 to 4 post-infarction, McClish et al. (61) found similar FFR in 43 vessels subtending recent infarct beds compared with 25 control vessels, matched by lesion length and minimal luminal diameter, in patients without infarcts (0.67 ± 17 vs. 0.68 ± 17 , $p = \text{NS}$). However, noninvasive physiologic evaluation was not performed. Therefore, in a subsequent study, Samady et al. (36) compared FFR with SPECT and myocardial contrast echo in 48 patients 3.7 ± 1.3 days after infarction. To identify true reversibility, follow-up SPECT was performed 11 weeks after PCI. The sensitivity, specificity, and concordance of $\text{FFR} \leq 0.75$ for detecting true reversibility on SPECT were 88%, 93%, and 91% (chi-square $p < 0.001$) and for detecting reversibility on myocardial contrast echo were 90%, 100%, and 93% (chi-square $p < 0.001$), respectively (Fig. 11). The optimal FFR value for discriminating inducible ischemia on noninvasive imaging was also 0.78, similar to DeBruyne et al. (35).

Fearon et al. (38) found that patients with preserved IMR after primary angioplasty may have greater recovery of regional ventricular function after primary angioplasty for ST-segment elevation myocardial infarction. In addition to providing prognostic information in this important patient subset, IMR may potentially be used in selecting patients

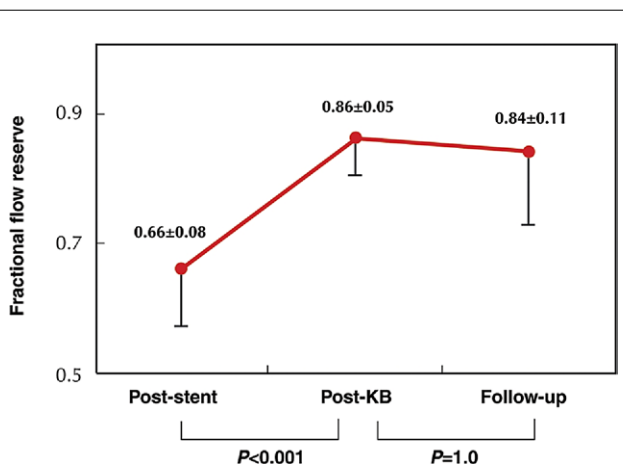
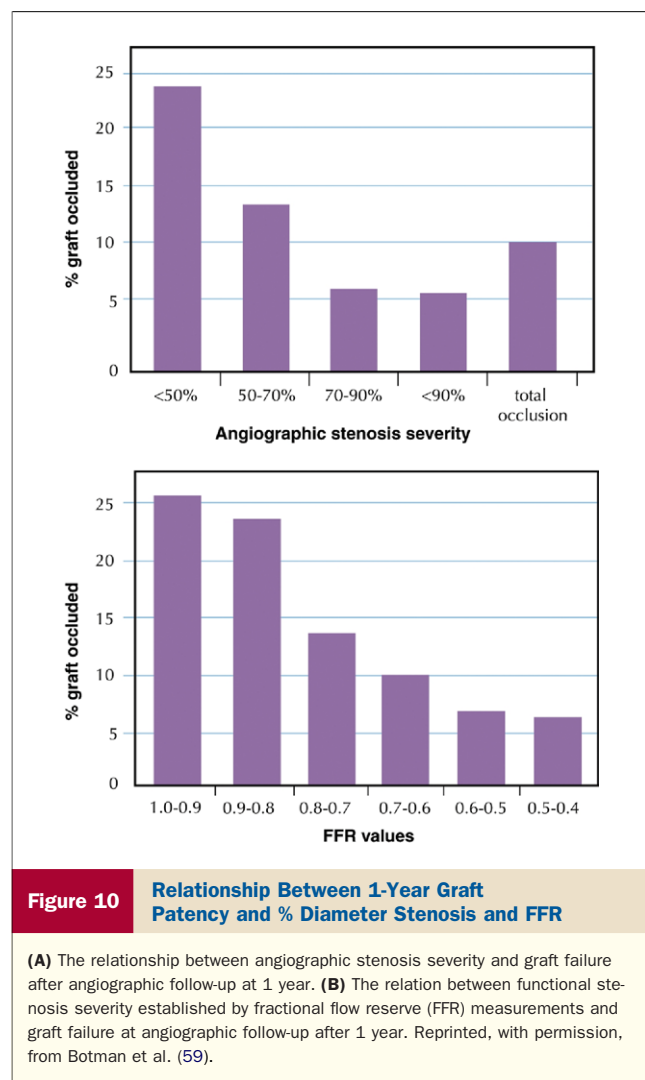


Figure 9 FFR and Jailed Side Branch Follow-Up

Serial changes of fractional flow reserve (FFR) in the side branch vessel of 22 bifurcation lesions after stenting main vessel (Post-stent), after kissing balloon inflation of main vessel and side branch (Post-KB), and at 6 months' follow-up. Reprinted, with permission, from Koo et al. (58).



with relatively preserved post-infarct microvasculature that might most benefit from regional delivery of regenerative cell therapies.

The use of FFR to reduce cost in ACS patient management was reported by Leesar et al. (62), who randomized 70 patients with recent unstable angina or non-ST-segment elevation myocardial infarction with intermediate single-vessel stenosis to 1 of 2 strategies: angiography followed by SPECT the next day or FFR-guided revascularization at the time of angiography. Compared with the SPECT strategy, the FFR-guided approach had a reduced hospital duration (11 ± 2 h vs. 49 ± 5 h, $p < 0.001$) and cost (U.S. $\$1,329 \pm \44 vs. $\$2,113 \pm \120 , $p < 0.05$), with no increase in procedure time, radiation exposure time, or clinical event rates at 1 year of follow-up. Similarly, Potvin et al. (63) evaluated 201 consecutive patients (62% with unstable angina or MI) in whom revascularization was guided by FFR. At 11 ± 6 months of follow-up, cardiac events occurred in 20 patients (10%), and no significant differences were observed between patients with unstable angina or MI and those with stable angina (9% vs. 13%, $p = 0.44$). Finally, Fischer et al. (64)

found similar MACE rates at 12 months in patients with ($n = 35$) and without ($n = 85$) ACS in whom revascularization was guided by FFR (15% vs. 9%, $p = \text{NS}$).

Summary

Integrating coronary physiology in the cardiac cath lab, principally using FFR, represents a precise and powerful adjunctive tool complementing angiography and providing

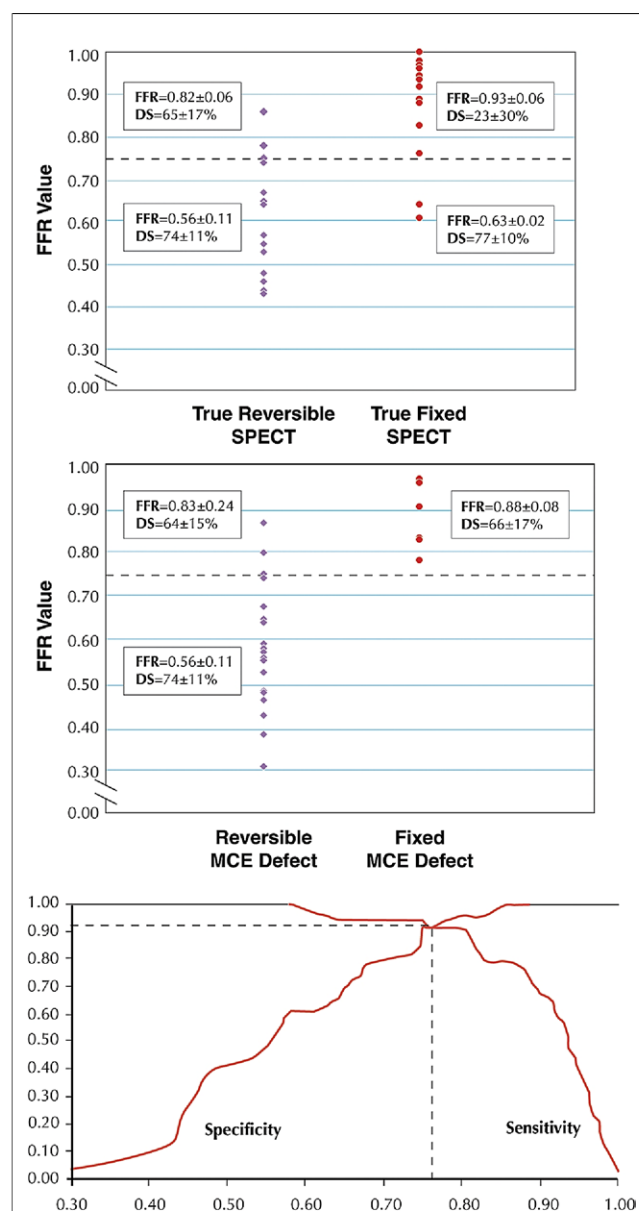


Figure 11 FFR, SPECT, and MCE in the Early Post-Myocardial Infarction Patient

(A) Concordance between fractional flow reserve (FFR) and single-photon emission computed tomography (SPECT) (dipyridamole-stress paired with rest imaging). (B) Concordance between FFR and myocardial contrast echo (MCE). (C) Sensitivity and specificity curves of FFR for detecting reversibility of combined noninvasive testing in patients with acute coronary syndrome. Reprinted, with permission, from Samady et al. (36). DS = diameter stenosis.

objective data about specific lesions and their ischemic potential. FFR is considered one of the standards for functional assessment of CAD, acting as a stress test within the cardiac cath lab environment. Although the cost of the physiologic information translates into an operational expense for the cath lab, the data identify significant overall savings to the health care system and a substantial clinical benefit to the patient.

Although FFR use in the cath lab has steadily grown over the past decade, and given the strong case for favorable outcomes, it is surprising that FFR is not more widely applied. Reluctance to adopt the technique is multifactorial, including habit, bias, training experience, practice pressures of patient throughput, financial incentives, and misconceptions by patients, families, and referring physicians regarding the perceived need to stent CAD. FFR technology hurdles of cumbersome set-up time, accurate hemodynamics, and dosing of adenosine have contributed to slow adoption of FFR in some laboratories. These issues have been overcome in laboratories with insightful physician and cath lab team member concept adopters. Physiologic data acquired during the angiographic procedure can facilitate timely, clinically, and economically sound decision making to direct revascularization options for best patient outcomes.

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